IN THE DRAWINGS

Enclosed are substitute drawing sheets of Figures 4, 5, 6, 9 and 12, as well as a marked up copy of each of these figures, showing the changes made in red ink. Specifically, Figures 4-6 and 12 are amended herein to add sequence identifiers to the amino acid sequences shown in these figures. Also, Figure 9 is amended to remove the symbol @ and replace it with the word "at" and Figures 9 and 10 are redrawn to insert arrows rather than lines to indicate the steps shown.

In addition, Figure 5 and Figure 12 are amended herein to correct an error in the amino acid sequence shown for the human 4E-BP1 peptide. Specifically, there is a U at the end of this amino acid sequence that would readily be recognized by one of ordinary skill in the art to be an error and the amino acid sequence for human 4E-BP1 as shown in Accession No. NP_004086 in the GenBank database (copy enclosed) has a C at this position, rather than a U. Thus, this peptide is amended from RIIYDRKFLMEU to RIIYDRKFLMEC to correct this inadvertent typographical error. No new matter is added by this amendment, as applicants are merely correcting the sequence to match the published amino acid sequence for this peptide.

Please enter these substitute drawing sheets into the present application and replace the previously submitted corresponding drawing sheets therewith.

REMARKS

Claims 11-22 are pending in this application. Claims 15 and 19-22 are withdrawn as directed to a non-elected invention. Claims 13 and 17 are canceled herein without prejudice. Claims 11, 12, 14, 16 and 18 are amended herein to more particularly define the invention. Figures 4, 5, 6, 9 and 12 are amended herein to include sequence identifiers, address other objections raised by the Examiner and to correct an obvious error in the amino acid sequence of the 4E-BP1 peptide, as described herein. Support for these amendments is found in the language of the original claims and throughout the specification, as set forth below. No new matter is added by these amendments and their entry and consideration are respectfully requested.

STATEMENT IN SUPPORT OF FILING A SUBSTITUTE SEQUENCE LISTING UNDER 37 CFR § 1.821(f)

I hereby state that the content of the paper and computer readable copies of the Substitute Sequence listing, submitted concurrently herewith in accordance with 37 CFR § 1.821(c) and (e), is the same. I also hereby state as required by 37 CFR § 1.821(h) that the paper and computer readable copies contain no new matter, nor do they go beyond the disclosure of the application as filed.

RECORDATION OF INTERVIEW SUMMARY IN ACCORDANCE WITH M.P.E.P. § 713.04

Applicants wish to make of record the Interview Summary prepared and submitted to applicants by Examiner Yu on April 21, 2006. Applicants concur that this Interview Summary accurately reflects the substance of the telephone interview on April 14, 2006 in which Examiner Yu and applicants' representative, Dr. Mary Miller, participated. Applicants appreciate the opportunity to discuss this application and pending claims with the Examiner.

I. Objections

A. The Office Action states that claims 11-12 and 16-18 are objected to for lacking sequence identifiers.

Claims 11-12, 16 and 18 are amended herein to include sequence identifiers, thereby mooting this objection.

B. The Office Action states that Figures 4-6 and 12 are objected to for lacking sequence identifiers. Figures 9 and 10 are objected to due to the presence of cross lines over inserts. Figure 9 is further objected to for use of the symbol @.

Substitute sheets of Figures 4-6 and 12 are provided herewith, wherein the figures are amended to include sequence identifiers, show arrows instead of cross lines and to remove the symbol @, thereby mooting this rejection.

II. Rejection under 35 U.S.C. § 112, second paragraph

A. The Office Action states that claims 11 and 16-18 are rejected as allegedly indefinite for use of the phrase "variable amino acid."

Claims 11, 16 and 18 are amended herein to recite that x is any amino acid, a synthetic amino acid or an unnatural-amino acid, rather than a variable amino acid. Support for this amendment is found throughout the specification, for example, on page 4, lines 24-26. Claim 17 is canceled herein without prejudice. The pending claims are now definite in the recitation of x and applicants respectfully request the withdrawal of this rejection.

B. The Office Action states that claim 12 lacks antecedent basis due to the recitation of amino acid sequences "RVRYSDQLLDL" and "RIIYDRKL," which the Examiner states do not read on the sequence set forth in claim 11.

Claim 12 is amended herein to recite the method according to claim 11, wherein said peptide comprises the sequence: KKRYDREFLLGF (SEQ ID NO:1); RVRYSRDQLLDL (SEQ ID NO:2); or RIIYDRKFL(L/M) (SEQ ID NO:3). Support for these amendments can be found in the specification, for example, on page 4, lines 9-11. The amino acid sequences of claim 12

now have proper antecedent basis from claim 11 and applicants respectfully request the withdrawal of this rejection.

C. The Office Action states that claims 13, 16 and 18 are allegedly indefinite as lacking antecedent basis because a peptide of 7-9 residues does not read on the length of the amino acid sequence of claim 11, which has 10 amino acids.

Claim 13 is canceled herein without prejudice and claims 11, 16 and 18 are amended herein to recite a peptide of 10-25 amino acids, thereby providing proper antecedent basis. Support for this amendment is found in the original claim language and in the specification, for example, on page 7, lines 18-20. Thus, applicants respectfully request the withdrawal of this rejection.

III. Rejection under 35 U.S.C. § 103

The Office Action states that claims 11-12, 14 and 17 are rejected under 35 U.S.C. § 103 as allegedly obvious over Hentze et al., in combination with the statement on page 4 of the specification, that a peptide of eIF4G residues 569-580 is capable of inducing programmed cell death.

Applicants respectfully point out that the invention disclosed in Hentze et al. is based on the discovery that the core region (residues 642-1091) of human eIF4Gq functions as an autonomous ribosome recruitment core *in vivo* (column 4, lines 47-51) and the invention described therein provides methods and means to detect and isolate the genes encoding RNA binding proteins (column 4, lines 62-64). In particular, it is noted that although Hentze et al. mentions the eIF4E binding domain of eIF4G, it is referred to as an optional domain (column 15, lines 11012), which in preferred embodiments, is deleted from the claimed fusion protein.

Thus, the disclosure of Hentze et al. does not teach or suggest a method in which small (e.g., 10-25 amino acid) peptides are used to induce programmed cell death in, for example, tumours and thus, the present invention would not have been obvious to one of ordinary skill in

the art at the time this invention was made on the basis of Hentze et al. However, in order to expedite prosecution of the pending claims to issue, claim 11 is amended herein to recite a peptide of 10-25 amino acids, thus incorporating a size limitation as set forth in claims 16 and 18, which are not rejected as obvious in the present Office Action. Support for this amendment is found in the original claim language and in the specification, for example, on page 7, lines 18-20. Thus, this rejection has been overcome and applicants respectfully request its withdrawal and allowance of the pending claims to issue.

Having addressed all of the issues raised the Examiner, applicants believe this application is in condition for allowance, which action is respectfully requested. The Examiner is encouraged to contact the undersigned directly if such contact will expedite the allowance of the pending claims to issue.

A check in the amount of $450.00 for a two month extension of time is included with this response. This amount is believed to be correct. However, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

Mary L. Miller

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Amelia Tauchen

☐ 1: NP_004086. Reports eukaryotic transl...[gi:4758258]

BLink, Conserved Domains, Links

Comment Features Sequence

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LOCUS       NP_004086                 118 aa            linear   PRI 06-NOV-2005
DEFINITION  eukaryotic translation initiation factor 4E binding protein 1 [Homo
            sapiens].
ACCESSION   NP_004086
VERSION     NP_004086.1  GI:4758258
DBSOURCE    REFSEQ: accession NM_004095.2
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 118)
  AUTHORS   Li,X., Alafuzoff,I., Soininen,H., Winblad,B. and Pei,J.J.
  TITLE     Levels of mTOR and its downstream targets 4E-BP1, eEF2, and eEF2
            kinase in relationships with tau in Alzheimer's disease brain
  JOURNAL   FEBS J. 272 (16), 4211-4220 (2005)
   PUBMED   16098202
  REMARK    GeneRIF: levels of p-mTOR (Ser2481), and p-4E-BP1 (Thr70 and Ser65)
            dramatically increase in Alzheimer disease, and are positively
            significantly correlated with total tau and p-tau
REFERENCE   2  (residues 1 to 118)
  AUTHORS   Shenberger,J.S., Myers,J.L., Zimmer,S.G., Powell,R.J. and
            Barchowsky,A.
  TITLE     Hyperoxia alters the expression and phosphorylation of multiple
            factors regulating translation initiation
  JOURNAL   Am. J. Physiol. Lung Cell Mol. Physiol. 288 (3), L442-L449 (2005)
   PUBMED   15542544
  REMARK    GeneRIF: These findings suggest that hyperoxia diminishes protein
            synthesis by increasing eIF4E phosphorylation and enhancing the
            affinity of 4E-BP1 for eIF4E.
REFERENCE   3  (residues 1 to 118)
  AUTHORS   Foukas,L.C. and Shepherd,P.R.
  TITLE     eIF4E binding protein 1 and H-Ras are novel substrates for the
            protein kinase activity of class-I phosphoinositide 3-kinase
  JOURNAL   Biochem. Biophys. Res. Commun. 319 (2), 541-549 (2004)
   PUBMED   15178440
  REMARK    GeneRIF: role as physiological substrates for the protein kinase
            activity of PI 3-kinase and suggests this activity operates in a
            physiological context by phosphorylating substrates other than the
            PI 3-kinase itself
REFERENCE   4  (residues 1 to 118)
  AUTHORS   Tee,A.R., Tee,J.A. and Blenis,J.
  TITLE     Characterizing the interaction of the mammalian eIF4E-related
```

protein 4EHP with 4E-BP1
JOURNAL FEBS Lett. 564 (1-2), 58-62 (2004)
PUBMED 15094042
REMARK GeneRIF: 4EHP over-expression instigates a negative feedback loop that inhibits upstream signaling to 4E-BP1 and ribosomal protein S6 kinase 1 (S6K1) whereas the 4E-BP1-binding-deficient mutant of 4EHP(W95A) was unable to trigger this feedback loop
REFERENCE 5 (residues 1 to 118)
AUTHORS Ferguson,G., Mothe-Satney,I. and Lawrence,J.C. Jr.
TITLE Ser-64 and Ser-111 in PHAS-I are dispensable for insulin-stimulated dissociation from eIF4E
JOURNAL J. Biol. Chem. 278 (48), 47459-47465 (2003)
PUBMED 14507920
REMARK GeneRIF: Ser-64 and Ser-111 are not required for the control of PHAS-I binding to eIF4E in cells, implicating phosphorylation of the Thr sites in dissociation of the PHAS-I.eIF4E complex
REFERENCE 6 (residues 1 to 118)
AUTHORS Beugnet,A., Wang,X. and Proud,C.G.
TITLE Target of rapamycin (TOR)-signaling and RAIP motifs play distinct roles in the mammalian TOR-dependent phosphorylation of initiation factor 4E-binding protein 1
JOURNAL J. Biol. Chem. 278 (42), 40717-40722 (2003)
PUBMED 12912989
REMARK GeneRIF: TOR-signaling and RAIP motifs play distinct roles in the mammalian TOR-dependent phosphorylation of initiation factor 4E-binding protein 1
REFERENCE 7 (residues 1 to 118)
AUTHORS Lekmine,F., Uddin,S., Sassano,A., Parmar,S., Brachmann,S.M., Majchrzak,B., Sonenberg,N., Hay,N., Fish,E.N. and Platanias,L.C.
TITLE Activation of the p70 S6 kinase and phosphorylation of the 4E-BP1 repressor of mRNA translation by type I interferons
JOURNAL J. Biol. Chem. 278 (30), 27772-27780 (2003)
PUBMED 12759354
REMARK GeneRIF: 4EBP1 is activated by the Type I IFN receptor-activated PI 3'-kinase pathway and has a role in regulating mRNA translation and induction of Type I IFN responses
REFERENCE 8 (residues 1 to 118)
AUTHORS Garami,A., Zwartkruis,F.J., Nobukuni,T., Joaquin,M., Roccio,M., Stocker,H., Kozma,S.C., Hafen,E., Bos,J.L. and Thomas,G.
TITLE Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2
JOURNAL Mol. Cell 11 (6), 1457-1466 (2003)
PUBMED 12820960
REMARK GeneRIF: Rheb is a mediator of 4EBP1.
REFERENCE 9 (residues 1 to 118)
AUTHORS Choi,K.M., McMahon,L.P. and Lawrence,J.C. Jr.
TITLE Two motifs in the translational repressor PHAS-I required for efficient phosphorylation by mammalian target of rapamycin and for recognition by raptor
JOURNAL J. Biol. Chem. 278 (22), 19667-19673 (2003)
PUBMED 12665511
REFERENCE 10 (sites)
AUTHORS Choi,K.M., McMahon,L.P. and Lawrence,J.C. Jr.
TITLE Two motifs in the translational repressor PHAS-I required for efficient phosphorylation by mammalian target of rapamycin and for recognition by raptor
JOURNAL J Biol Chem 278 (22), 19667-19673 (2003)
PUBMED 12665511
REFERENCE 11 (residues 1 to 118)
AUTHORS Rolli-Derkinderen,M., Machavoine,F., Baraban,J.M., Grolleau,A., Beretta,L. and Dy,M.
TITLE ERK and p38 inhibit the expression of 4E-BP1 repressor of

translation through induction of Egr-1
JOURNAL J. Biol. Chem. 278 (21), 18859-18867 (2003)
PUBMED 12618431
REMARK GeneRIF: data demonstrates that eukaryotic translation initiation factor 4E binding protein 1 is a new target for early growth response-1
REFERENCE 12 (residues 1 to 118)
AUTHORS Nojima,H., Tokunaga,C., Eguchi,S., Oshiro,N., Hidayat,S., Yoshino,K., Hara,K., Tanaka,N., Avruch,J. and Yonezawa,K.
TITLE The mammalian target of rapamycin (mTOR) partner, raptor, binds the mTOR substrates p70 S6 kinase and 4E-BP1 through their TOR signaling (TOS) motif
JOURNAL J. Biol. Chem. 278 (18), 15461-15464 (2003)
PUBMED 12604610
REMARK GeneRIF: raptor binds to p70S6k and 4E-BP1 through their respective TOS (conserved TOR signaling) motifs.
REFERENCE 13 (residues 1 to 118)
AUTHORS Wang,X., Li,W., Parra,J.L., Beugnet,A. and Proud,C.G.
TITLE The C terminus of initiation factor 4E-binding protein 1 contains multiple regulatory features that influence its function and phosphorylation
JOURNAL Mol. Cell. Biol. 23 (5), 1546-1557 (2003)
PUBMED 12588975
REMARK GeneRIF: 4E-binding protein 1 C terminus has domains that control function and phosphorylation
REFERENCE 14 (sites)
AUTHORS Wang,X., Li,W., Parra,J.L., Beugnet,A. and Proud,C.G.
TITLE The C terminus of initiation factor 4E-binding protein 1 contains multiple regulatory features that influence its function and phosphorylation
JOURNAL Mol Cell Biol 23 (5), 1546-1557 (2003)
PUBMED 12588975
REFERENCE 15 (residues 1 to 118)
AUTHORS Tee,A.R., Fingar,D.C., Manning,B.D., Kwiatkowski,D.J., Cantley,L.C. and Blenis,J.
TITLE Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 99 (21), 13571-13576 (2002)
PUBMED 12271141
REMARK GeneRIF: hamartin and tuberin function together to inhibit mammalian target of rapamycin (mTOR)-mediated signaling to eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and ribosomal protein S6 kinase 1 (S6K1)
REFERENCE 16 (residues 1 to 118)
AUTHORS Chung,J., Bachelder,R.E., Lipscomb,E.A., Shaw,L.M. and Mercurio,A.M.
TITLE Integrin (alpha 6 beta 4) regulation of eIF-4E activity and VEGF translation: a survival mechanism for carcinoma cells
JOURNAL J. Cell Biol. 158 (1), 165-174 (2002)
PUBMED 12105188
REFERENCE 17 (sites)
AUTHORS Chung,J., Bachelder,R.E., Lipscomb,E.A., Shaw,L.M. and Mercurio,A.M.
TITLE Integrin (alpha 6 beta 4) regulation of eIF-4E activity and VEGF translation: a survival mechanism for carcinoma cells
JOURNAL J Cell Biol 158 (1), 165-174 (2002)
PUBMED 12105188
REFERENCE 18 (residues 1 to 118)
AUTHORS Fingar,D.C., Salama,S., Tsou,C., Harlow,E. and Blenis,J.
TITLE Mammalian cell size is controlled by mTOR and its downstream targets S6K1 and 4EBP1/eIF4E

JOURNAL Genes Dev. 16 (12), 1472-1487 (2002)
PUBMED 12080086
REMARK GeneRIF: Mammalian cell size is controlled by mTOR and its downstream targets S6K1 and 4EBP1/eIF4E
REFERENCE 19 (residues 1 to 118)
AUTHORS Dilling,M.B., Germain,G.S., Dudkin,L., Jayaraman,A.L., Zhang,X., Harwood,F.C. and Houghton,P.J.
TITLE 4E-binding proteins, the suppressors of eukaryotic initiation factor 4E, are down-regulated in cells with acquired or intrinsic resistance to rapamycin
JOURNAL J. Biol. Chem. 277 (16), 13907-13917 (2002)
PUBMED 11847216
REMARK GeneRIF: 4E-binding proteins, the suppressors of eukaryotic initiation factor 4E, are down-regulated in cells with acquired or intrinsic resistance to rapamycin.
REFERENCE 20 (residues 1 to 118)
AUTHORS Li,S., Sonenberg,N., Gingras,A.C., Peterson,M., Avdulov,S., Polunovsky,V.A. and Bitterman,P.B.
TITLE Translational control of cell fate: availability of phosphorylation sites on translational repressor 4E-BP1 governs its proapoptotic potency
JOURNAL Mol. Cell. Biol. 22 (8), 2853-2861 (2002)
PUBMED 11909977
REMARK GeneRIF: Translational control of cell fate: availability of phosphorylation sites on translational repressor 4E-BP1 governs its proapoptotic potency.
REFERENCE 21 (residues 1 to 118)
AUTHORS Liu,G., Zhang,Y., Bode,A.M., Ma,W.Y. and Dong,Z.
TITLE Phosphorylation of 4E-BP1 is mediated by the p38/MSK1 pathway in response to UVB irradiation
JOURNAL J. Biol. Chem. 277 (11), 8810-8816 (2002)
PUBMED 11777913
REFERENCE 22 (sites)
AUTHORS Liu,G., Zhang,Y., Bode,A.M., Ma,W.Y. and Dong,Z.
TITLE Phosphorylation of 4E-BP1 is mediated by the p38/MSK1 pathway in response to UVB irradiation
JOURNAL J Biol Chem 277 (11), 8810-8816 (2002)
PUBMED 11777913
REFERENCE 23 (residues 1 to 118)
AUTHORS Gingras,A.C., Raught,B., Gygi,S.P., Niedzwiecka,A., Miron,M., Burley,S.K., Polakiewicz,R.D., Wyslouch-Cieszynska,A., Aebersold,R. and Sonenberg,N.
TITLE Hierarchical phosphorylation of the translation inhibitor 4E-BP1
JOURNAL Genes Dev. 15 (21), 2852-2864 (2001)
PUBMED 11691836
REFERENCE 24 (sites)
AUTHORS Gingras,A.C., Raught,B., Gygi,S.P., Niedzwiecka,A., Miron,M., Burley,S.K., Polakiewicz,R.D., Wyslouch-Cieszynska,A., Aebersold,R. and Sonenberg,N.
TITLE Hierarchical phosphorylation of the translation inhibitor 4E-BP1
JOURNAL Genes Dev 15 (21), 2852-2864 (2001)
PUBMED 11691836
REFERENCE 25 (residues 1 to 118)
AUTHORS Shen,X., Tomoo,K., Uchiyama,S., Kobayashi,Y. and Ishida,T.
TITLE Structural and thermodynamic behavior of eukaryotic initiation factor 4E in supramolecular formation with 4E-binding protein 1 and mRNA cap analogue, studied by spectroscopic methods
JOURNAL Chem. Pharm. Bull. 49 (10), 1299-1303 (2001)
PUBMED 11605658
REFERENCE 26 (residues 1 to 118)
AUTHORS Ito,M., Shichijo,S., Tsuda,N., Ochi,M., Harashima,N., Saito,N. and Itoh,K.

TITLE Molecular basis of T cell-mediated recognition of pancreatic cancer cells
JOURNAL Cancer Res. 61 (5), 2038-2046 (2001)
PUBMED 11280764
REFERENCE 27 (residues 1 to 118)
AUTHORS Kim,J.E. and Chen,J.
TITLE Cytoplasmic-nuclear shuttling of FKBP12-rapamycin-associated protein is involved in rapamycin-sensitive signaling and translation initiation
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 97 (26), 14340-14345 (2000)
PUBMED 11114166
REFERENCE 28 (residues 1 to 118)
AUTHORS Yang,D.Q. and Kastan,M.B.
TITLE Participation of ATM in insulin signalling through phosphorylation of eIF-4E-binding protein 1
JOURNAL Nat. Cell Biol. 2 (12), 893-898 (2000)
PUBMED 11146653
REFERENCE 29 (sites)
AUTHORS Yang,D.Q. and Kastan,M.B.
TITLE Participation of ATM in insulin signalling through phosphorylation of eIF-4E-binding protein 1
JOURNAL Nat Cell Biol 2 (12), 893-898 (2000)
PUBMED 11146653
REFERENCE 30 (residues 1 to 118)
AUTHORS Mothe-Satney,I., Brunn,G.J., McMahon,L.P., Capaldo,C.T., Abraham,R.T. and Lawrence,J.C. Jr.
TITLE Mammalian target of rapamycin-dependent phosphorylation of PHAS-I in four (S/T)P sites detected by phospho-specific antibodies
JOURNAL J. Biol. Chem. 275 (43), 33836-33843 (2000)
PUBMED 10942774
REFERENCE 31 (sites)
AUTHORS Mothe-Satney,I., Brunn,G.J., McMahon,L.P., Capaldo,C.T., Abraham,R.T. and Lawrence,J.C. Jr.
TITLE Mammalian target of rapamycin-dependent phosphorylation of PHAS-I in four (S/T)P sites detected by phospho-specific antibodies
JOURNAL J Biol Chem 275 (43), 33836-33843 (2000)
PUBMED 10942774
REFERENCE 32 (residues 1 to 118)
AUTHORS Mothe-Satney,I., Yang,D., Fadden,P., Haystead,T.A. and Lawrence,J.C. Jr.
TITLE Multiple mechanisms control phosphorylation of PHAS-I in five (S/T)P sites that govern translational repression
JOURNAL Mol. Cell. Biol. 20 (10), 3558-3567 (2000)
PUBMED 10779345
REFERENCE 33 (sites)
AUTHORS Mothe-Satney,I., Yang,D., Fadden,P., Haystead,T.A. and Lawrence,J.C. Jr.
TITLE Multiple mechanisms control phosphorylation of PHAS-I in five (S/T)P sites that govern translational repression
JOURNAL Mol Cell Biol 20 (10), 3558-3567 (2000)
PUBMED 10779345
REFERENCE 34 (residues 1 to 118)
AUTHORS Gingras,A.C., Gygi,S.P., Raught,B., Polakiewicz,R.D., Abraham,R.T., Hoekstra,M.F., Aebersold,R. and Sonenberg,N.
TITLE Regulation of 4E-BP1 phosphorylation: a novel two-step mechanism
JOURNAL Genes Dev. 13 (11), 1422-1437 (1999)
PUBMED 10364159
REFERENCE 35 (sites)
AUTHORS Gingras,A.C., Gygi,S.P., Raught,B., Polakiewicz,R.D., Abraham,R.T., Hoekstra,M.F., Aebersold,R. and Sonenberg,N.
TITLE Regulation of 4E-BP1 phosphorylation: a novel two-step mechanism
JOURNAL Genes Dev 13 (11), 1422-1437 (1999)

PUBMED 10364159
REFERENCE 36 (residues 1 to 118)
AUTHORS Heesom,K.J., Avison,M.B., Diggle,T.A. and Denton,R.M.
TITLE Insulin-stimulated kinase from rat fat cells that phosphorylates initiation factor 4E-binding protein 1 on the rapamycin-insensitive site (serine-111)
JOURNAL Biochem. J. 336 (PT 1), 39-48 (1998)
PUBMED 9806882
REFERENCE 37 (sites)
AUTHORS Heesom,K.J., Avison,M.B., Diggle,T.A. and Denton,R.M.
TITLE Insulin-stimulated kinase from rat fat cells that phosphorylates initiation factor 4E-binding protein 1 on the rapamycin-insensitive site (serine-111)
JOURNAL Biochem J 336 (PT 1), 39-48 (1998)
PUBMED 9806882
REFERENCE 38 (residues 1 to 118)
AUTHORS New,L., Jiang,Y., Zhao,M., Liu,K., Zhu,W., Flood,L.J., Kato,Y., Parry,G.C. and Han,J.
TITLE PRAK, a novel protein kinase regulated by the p38 MAP kinase
JOURNAL EMBO J. 17 (12), 3372-3384 (1998)
PUBMED 9628874
REFERENCE 39 (residues 1 to 118)
AUTHORS Burnett,P.E., Barrow,R.K., Cohen,N.A., Snyder,S.H. and Sabatini,D.M.
TITLE RAFT1 phosphorylation of the translational regulators p70 S6 kinase and 4E-BP1
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 95 (4), 1432-1437 (1998)
PUBMED 9465032
REFERENCE 40 (sites)
AUTHORS Burnett,P.E., Barrow,R.K., Cohen,N.A., Snyder,S.H. and Sabatini,D.M.
TITLE RAFT1 phosphorylation of the translational regulators p70 S6 kinase and 4E-BP1
JOURNAL Proc Natl Acad Sci U S A 95 (4), 1432-1437 (1998)
PUBMED 9465032
REFERENCE 41 (residues 1 to 118)
AUTHORS Brunn,G.J., Fadden,P., Haystead,T.A. and Lawrence,J.C. Jr.
TITLE The mammalian target of rapamycin phosphorylates sites having a (Ser/Thr)-Pro motif and is activated by antibodies to a region near its COOH terminus
JOURNAL J. Biol. Chem. 272 (51), 32547-32550 (1997)
PUBMED 9405468
REFERENCE 42 (sites)
AUTHORS Brunn,G.J., Fadden,P., Haystead,T.A. and Lawrence,J.C. Jr.
TITLE The mammalian target of rapamycin phosphorylates sites having a (Ser/Thr)-Pro motif and is activated by antibodies to a region near its COOH terminus
JOURNAL J Biol Chem 272 (51), 32547-32550 (1997)
PUBMED 9405468
REFERENCE 43 (residues 1 to 118)
AUTHORS Fadden,P., Haystead,T.A. and Lawrence,J.C. Jr.
TITLE Identification of phosphorylation sites in the translational regulator, PHAS-I, that are controlled by insulin and rapamycin in rat adipocytes
JOURNAL J. Biol. Chem. 272 (15), 10240-10247 (1997)
PUBMED 9092573
REFERENCE 44 (sites)
AUTHORS Fadden,P., Haystead,T.A. and Lawrence,J.C. Jr.
TITLE Identification of phosphorylation sites in the translational regulator, PHAS-I, that are controlled by insulin and rapamycin in rat adipocytes
JOURNAL J Biol Chem 272 (15), 10240-10247 (1997)

PUBMED 9092573
REFERENCE 45 (residues 1 to 118)
AUTHORS Tsukiyama-Kohara,K., Vidal,S.M., Gingras,A.C., Glover,T.W., Hanash,S.M., Heng,H. and Sonenberg,N.
TITLE Tissue distribution, genomic structure, and chromosome mapping of mouse and human eukaryotic initiation factor 4E-binding proteins 1 and 2
JOURNAL Genomics 38 (3), 353-363 (1996)
PUBMED 8975712
REFERENCE 46 (residues 1 to 118)
AUTHORS Mader,S., Lee,H., Pause,A. and Sonenberg,N.
TITLE The translation initiation factor eIF-4E binds to a common motif shared by the translation factor eIF-4 gamma and the translational repressors 4E-binding proteins
JOURNAL Mol. Cell. Biol. 15 (9), 4990-4997 (1995)
PUBMED 7651417
REFERENCE 47 (residues 1 to 118)
AUTHORS Pause,A., Belsham,G.J., Gingras,A.C., Donze,O., Lin,T.A., Lawrence,J.C. Jr. and Sonenberg,N.
TITLE Insulin-dependent stimulation of protein synthesis by phosphorylation of a regulator of 5'-cap function
JOURNAL Nature 371 (6500), 762-767 (1994)
PUBMED 7935836
REFERENCE 48 (residues 1 to 118)
AUTHORS Haystead,T.A., Haystead,C.M., Hu,C., Lin,T.A. and Lawrence,J.C. Jr.
TITLE Phosphorylation of PHAS-I by mitogen-activated protein (MAP) kinase. Identification of a site phosphorylated by MAP kinase in vitro and in response to insulin in rat adipocytes
JOURNAL J. Biol. Chem. 269 (37), 23185-23191 (1994)
PUBMED 8083223
REFERENCE 49 (sites)
AUTHORS Haystead,T.A., Haystead,C.M., Hu,C., Lin,T.A. and Lawrence,J.C. Jr.
TITLE Phosphorylation of PHAS-I by mitogen-activated protein (MAP) kinase. Identification of a site phosphorylated by MAP kinase in vitro and in response to insulin in rat adipocytes
JOURNAL J Biol Chem 269 (37), 23185-23191 (1994)
PUBMED 8083223
COMMENT PROVISIONAL REFSEQ: This record has not yet been subject to final NCBI review. The reference sequence was derived from BC004459.1.
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Apr 11 2006 19:57:30

FIGURE 3

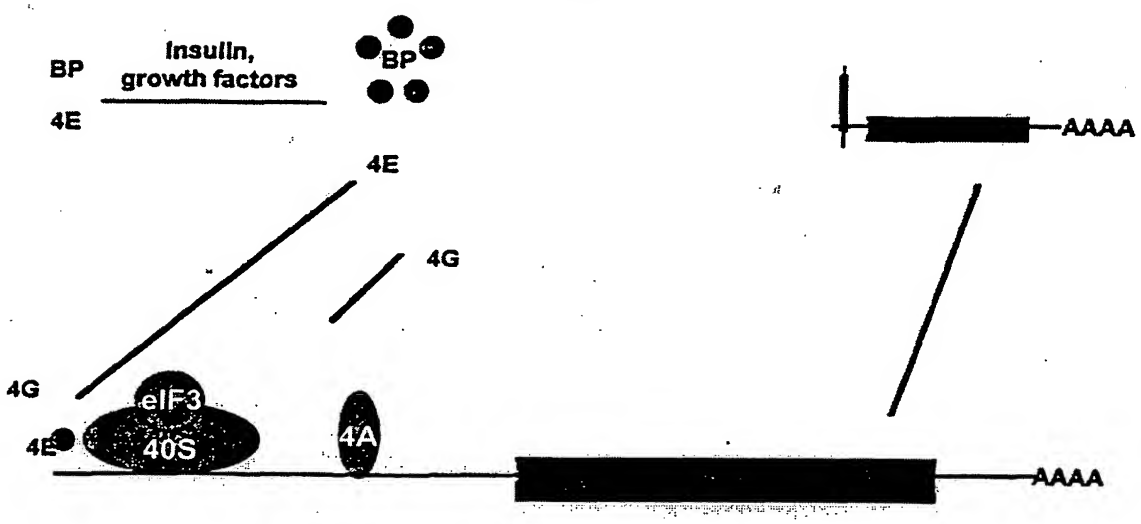
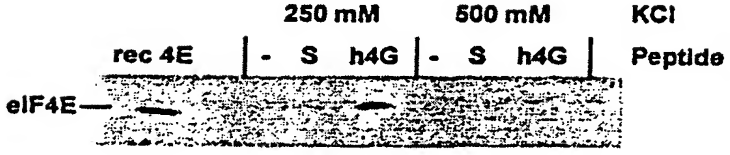


FIGURE 4



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S scrambled eIF4G B β FDLKFALGRYRAEKRQIKIWFQNRRMKWKK SEQ ID NO:8

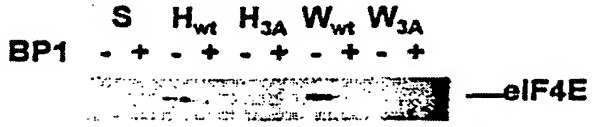
\- no peptide

rec 4E recombinant human eIF4E

FIGURE 5

H	human eIF4G	B β β K K R Y D R E F L L G F	413-424	SEQ ID NO:1
Y	yeast eIF4G	B β β K Y T Y G P T F L L Q F	449-460	SEQ ID NO:9
W	wheat eIF4G	B β β R V R Y S R D Q L L D L	62-73	SEQ ID NO:2
1	human 4E-BP1	B β β R I I Y D R K F L M E C	51-62	SEQ ID NO:10
2	human 4E-BP2	B β β R I I Y D R K F L L D R	51-62	SEQ ID NO:11
S	scrambled eIF4G			

FIGURE 6



	4G Peptide	Sequence	
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W_{wt}	wh $4G_{(62-73)}$	R V R Y S R D Q L L D L A A	SEQ ID NO:14
W_{3A}	wh $4G_{(62-73)YALALA}$	R V R A S R D Q A A D L A A	SEQ ID NO:15
S	scrambled hu 4G	F D L K F A L G R Y R A E K	SEQ ID NO:16

all peptides biotinylated and linked to Penetratin™

FIGURE 9

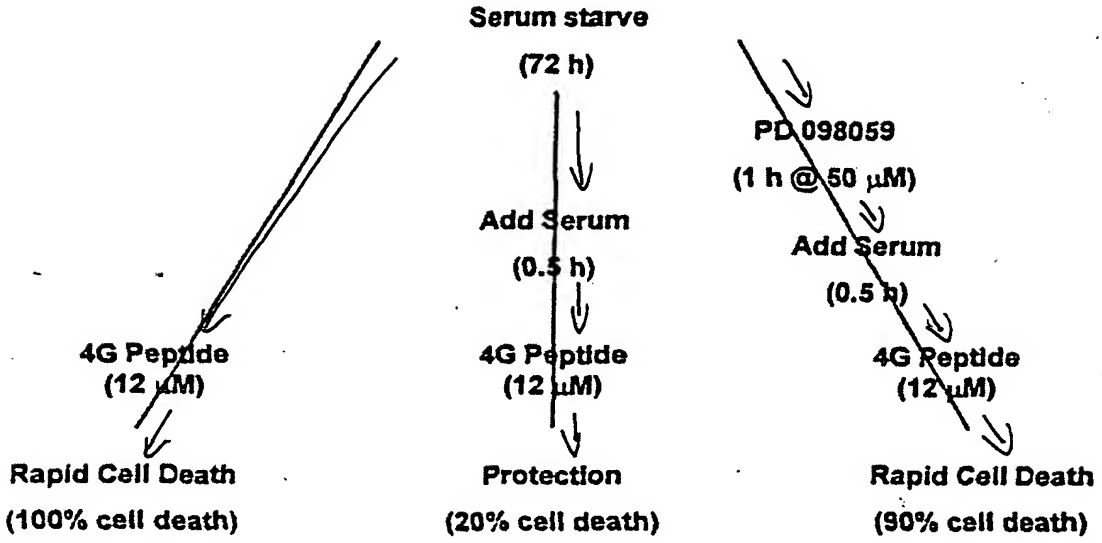

FIGURE 10

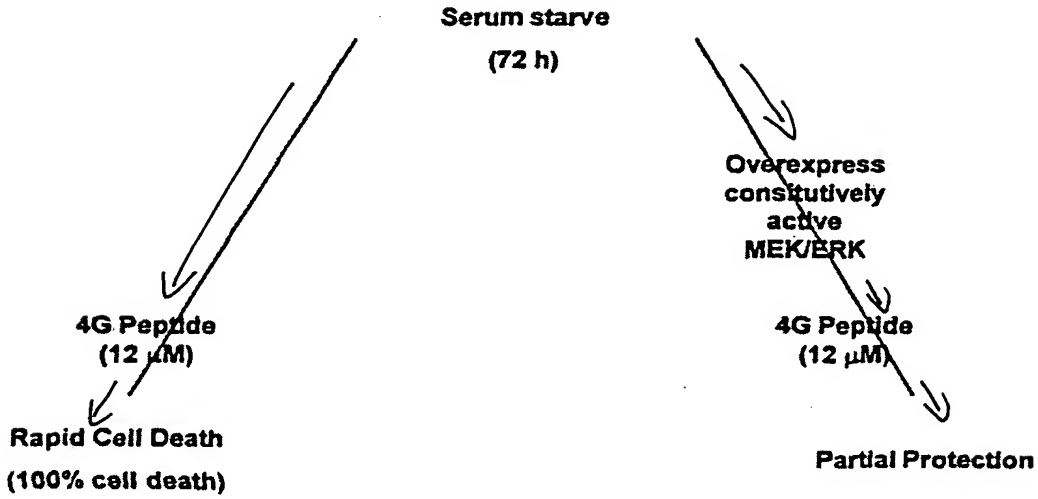

FIGURE 12

(a)

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Hu 4G Y-A	Human eIF4G Peptide (569-580)Y572A	KKRADREFLLGF SEQ ID NO:18
Hu 4G L-A	Human eIF4G Peptide (569-580)L577A	KKRYDREFALGF SEQ ID NO:19
W4G	Wheat eIF4G Peptide (62-73)Wild Type	RVRYSRDQLLDL SEQ ID NO:2
W4G YLL-AAA	Wheat eIF4G Peptide (62-73)Y65A, L70A, L71A	RVRASRDQAADL SEQ ID NO:20
BP2	Human 4E-BP2 Peptide (51-62)Wild Type	RIIYDRKFLLDR SEQ ID NO:11
BP2 YLL-AAA	Human 4E-BP2 Peptide (51-62)Y54A, L59A, L60A.	RIIADRKFAADR SEQ ID NO:21
BP1	Human 4E-BP1 Peptide (51-62)Wild Type	RIIYDRKFLMEV SEQ ID NO:10
BP1 YLM-AAA	Human 4E-BP1 Peptide (51-62)Y54A, L59A, M60A	RIIADRKFAAEV SEQ ID NO:22

(b)